Request for Continued Examination

The request filed on 11/21/2007 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 09402614 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims *1-26, 40-58, 60-63, 69, 72-93, 95, 96, 98 and 99* are pending.

Claims *1-26, 40-57, 61 and 92* are previously withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claims.

Claims *58, 60, 62, 63, 69, 72-91, 93, 95, 96, 98 and 99* are examined on the merits.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 11/28/2007 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Objection of Drawing

The drawings in this 371 application are submitted with the original PCT document. The Figures 4-8 are objected to because the quality of figures is not permitted for examination. Replacement of figures 4-8 is required in the reply for this action.

The informal drawings are not of sufficient quality to permit examination. Accordingly, replacement drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to this Office action. The replacement sheet(s) should be labeled “Replacement Sheet” in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement Rejection

Claims 58, 60, 62, 63, 69, 72-91, 93, 95, 96, 98 and 99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of screening a mammal comprising screening for the down regulation of “inhibin protein levels” wherein the down regulation of the inhibin protein levels relative to the inhibin protein levels of a normal mammal is indicative of the mammal having developed **prostate cancer** (Claim 58). The claimed method is further defined as a method of screening a mammal for prostate cancer comprising obtaining a biological sample and determining a level of an inhibin protein in said biological sample, and comparing said level to a normal mammal, wherein a down-regulation of said inhibin protein level in the biological sample relative to the inhibin protein level of a normal mammal is indicative of the mammal having developed prostate cancer (Claim 83 and 95). To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The objective of the claims is diagnosing or correlating developed prostate cancer with the down expression of protein inhibin. The specification does not define term “developed prostate cancer”, which is interpreted here as prostate cancer with different stages and

grade comprising metastasis. Thus, it would be expected that one of skill in the art would be able to diagnose the existed (developed) prostate cancer without undue a quantity of experimentations.

The specification teaches (page 43) the down-regulation or complete absence of inhibin subunit protein levels (αN and αC) in a small sampling (12 patients Gleason score 7-10, page 32) of human poorly differentiated prostate cancer tissues compared to the presence of αN and αC inhibin subunits in adjacent non-malignant regions of the prostate. Similarly, the specification teaches α-subunit gene expression was detected in basal cells in 7 of 8 patients in non-malignant regions while malignant tumor cells in adjacent regions of the same patient biopsies did not display any α-subunit gene expression. On page 3, line 1-10, the specification concludes that the tissues of benign prostatic hyperplasia, basal cell hyperplasia or in non-malignant regions of specimens from men with prostate cancer are stained for α-subnite of inhibin and In contrast, in malignant regions of tissue from men with advanced stage prostate cancer, inhibin α-subunit was down.

The states of the art have reported the expression of inhibin up or down regulated in the prostate cancer conditions. The correlation of the levels of inhibin or inhibin peptides to normal, hybperplasia, developed, metastatic, or the cancer stage of prostate are not clearly defined. For example, the previous Office Action dated 10/23/2006 has cited co-inventor Risbridger' recent publication (Risbridger *et al.* "**Re-evaulation** of inhibin α subunit as a tumour suppressor in prostate cancer". Molecular & Cellular Endocrinology, 2004, Vol. 225, pages 73-76, provided in the Office Action dated 1/20/2006), which suggests re-evaluating the role of inhibin in the prostate cancer condition as the following:

> An expanded study (approximately 174 prostate cancer specimens) of inhibin α subunit protein expression in prostate cancer revealed the opposite (abstract). That is, unexpectedly, in the majority of cases (89%) there was **more**, rather than less, intense staining of inhibin α subunit in cancer compared to the non-malignant tissue (page 75, 1st column). In their own words, the authors state (page 75, 1st column, 2nd full para.) "The results of the study were unexpected and did not support the previous evidence that inhibin α subunit was down regulated in men with prostate cancer."

On page 75, column 1, line 29-31, Risbridger et al., then conclude "the inhibin α-subunit was frequently over-expressed in high-grade prostate cancer. This is contradictory to the disclosure of the instant specification (page 3) stating "the α-subunit was down regulated in the malignant regions of tissue from men with advanced stage prostate. In the early study of expressing an inhibin peptide, Garde et al

(Cancer Lett. vol 78, page, 11-7 1994) collect 71 primary prostatic adenocarcinoma (PCA) and 5 cases of metastatic PCA with different Gleason scores ranged 2-10, and staining of the tissues are positive in all the cases of primary PCA and one bone metastasis (abstract). Zhang et al., (Hum Pathol vol 30 page 168-72, 1999) teach that although average percentage of cells expression prostate inhibin peptide (PIP) is decreased in prostatic intraepithelial neoplasia (PIN) when compared to benign prostatic hyperplasia (BPH) and normal tissues, There was no correlation of tumor PIP level with patient's age, tumor size, Gleason score, and tumor stage (abstract, line 18+). In the more recent study, Schaik et al., (British Journal of Cancer, col 82 page112-117, 2000) disclose that low or undetectable expression of α-subunit of inhibin in the primary prostate cancer (Gleason scored ranged from 1-8, page 113, col 2, figure 4, abstract, line 8).

Thus, based on the limited teaching of specification, insufficient evidence or direction/guideline provided, and preponderance of the evidences disclosed in the art, one of ordinary skill would believe that claimed method is merely an interesting invitation for the further research and believe that one skilled in the art could not use or practice claimed invention in a mammal comprising a human as claimed without undue a quantity of experimentations.

Previous response to applicant's argument dated 7/20/2006 is maintained for the reason of record as set forth in the Office action dated 10/23/2006.

Response to applicant's arguments

The response dated 11/27/2007 has been carefully considered but is deemed not to be persuasive. Applicant first describes the cancer as a progressive disease, which is defined by the grade based on the Gleason scores and then argues that metastatic stage may not correlate with a high grade or aggressive cancer (page 3). Applicant then argues (page 4, line 2+).

> the Examiner is assuming that we are claiming that all prostate cancers are characterized by a decrease in inhibin levels and are therefore diagnosable by virtue of screening for a decrease in inhibin levels. However, the claims are not directed to diagnosing prostate cancer, per se. Rather, they are directed to a method of screening a mammal wherein if one observes a decrease in inhibin protein level, then this is regarded as indicative of the mammal having developed prostate cancer. This is a significantly different position to that which the Examiner implies has been claimed since the claims as currently pending are not suggesting that all prostate cancers are diagnosable by virtue of screening for a down regulation of inhibin levels. Rather, they are

> indicating that where one observes a decrease in inhibin levels, this is indicative of that patient having developed prostate cancer.

Thus Applicant argues that the claimed method is not a method of diagnosing a prostate cancer; rather it is a method of screening for decrease in inhibin levels, which indicates the patient having developed prostate cancer. In response, first, the Office is confused and dose not see the difference in the scope of claimed method and preamble based on the claimed language. The Office would not clearly know what difference is between a method of diagnosing a prostate cancer by the decreased level of inhibin and a method of screening for decrease in inhibin levels correlating (indicating) a developed prostate cancer as argued above, the both method objectives are defining a prostate cancer by the decreased levels of inhibin. Secondly, if Applicant argues the difference between the two methods based on claimed languages, what is the intent use of claimed method of screening for decrease in inhibin levels, which indicates the patient having developed prostate cancer as instant claims? Once the decreased inhibin is determined in a prostate tissue, is the prostate tissue considered (correlated or diagnosed) as cancer tissue? In addition, based on the limited teaching of specification and the evidences disclosed in the art, one of ordinary skill would not be convinced that claimed method of screening a mammal for down regulation of inhibin protein could indicate the mammal having developed prostate cancer as stated above.

Applicant on page 5 further argues reference by Risbridger et al and the metastatic cancer, aggressive state and cancer grade stating:

> Not all the patients who develop prostate cancer may necessarily go on to develop metastatic cancer (line 1+).....As the cancer progresses into a highly aggressive state, inhibin levels are observed to become increased above normal levels. This is not inconsistent with the present application which merely discloses and claims the observation that levels of inhibin below normal are indicative of a mammal having developed prostate cancer (line 4+).
>
> This being the case, the claimed invention is entirely consistent with the Risbridger article, which merely presents the early data that ultimately led to the elucidation of the finding that inhibin levels do change at the time that a prostate cancer becomes highly aggressive, this being referred to as a "switch".

In response, claims reciting down regulation of inhibin indicating developed prostate cancer. The term “developed prostate cancer” is not clearly defined and seems exemplified as a high grade cancer in the specification (page 25, fig 8 and page 43). As stated in the rejection above, Risbridger et al., in his article

conclude that the inhibin α-subunit was frequently over-expressed in high-grade prostate cancer. As such, the Applicant is telling the Office that the term "high grade cancer" in the specification and co-inventor's own publication has the different meanings. However, based on the description of the specification, the teaching of Risbridgere et al., the Office does not have or gain such knowledge, which allows interpreting the claims reciting developed prostate cancer as a high grade cancer excluding the metastatic cancer. In addition, whether the claimed invention given a patentable weight is based on what is claims recited (language) in light of the teaching of the specification. Since the term "grade of cancer and "aggressive state of cancer" are not clearly defined in the specification and not appeared in the claims, one skilled in the art would not has the knowledge of or consider the term "developed prostate cancer" as high grade, aggressive prostate cancers, which do not include the metastatic prostate cancer.

Applicant also states the points of the interview dated on 4/27/2007, which have been covered in the response and enablement rejection above.

On page 6 (line 1+) Applicant further states:

> The fact that the prior art document indicates that the role of inhibin as a tumor suppressor requires re-evaluation is also not inconsistent with the present invention but merely indicates that the inventors have uncovered a degree of complexity in terms of the functioning of inhibin and that in fact the progression of prostate cancer can be delineated in more detail than was previously understood and therefore warrants further study. It does not, however, render incorrect or inconsistent the original findings that prostate cancer onset is associated with a decrease in inhibin levels and that wherever one does detect a decrease in inhibin levels, this is indicative of that patient having developed prostate cancer.

In response, as indicated and discussed above the function and role of inhibin in the prostate cancer with different grades or stages is complex, which has not been well described in the specification and the state of the arts. Reciting a simple method step in the claimed method to claim a complex subject matter, which is NOT covered or clearly stated in the claims and NOT well described in the specification does render the claims unpatentable because one skilled in the art would not know how to use or practice the claimed invention without undue a quantity of experimentations.

Applicant is invited to provide objective evidence to support claimed invention and clearly recite or define claimed invention by amending the claims. No new matter should be introduced. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

1. Claims 58, 60, 62, 63, 69, 72-91, 93, 95, 96, 98 and 99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-8 and 10 of copending Application No. **10551352 ('352)**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claim are directed to a method of enhancing cancer treatment by administering a compound of carbohydrate comprising modified pectin in combination of another chemotherapeutic agent, thus the claims are obvious over each other.

Instant claims are drawn to a method of screening a mammal comprising screening for the down regulation of "inhibin protein levels" wherein the down regulation of the inhibin protein levels relative to the inhibin protein levels of a normal mammal is indicative of the mammal having developed prostate cancer, wherein the inhbin is α-inhibin. The claimed method is further defined as a method of screening a mammal for prostate cancer comprising the step of obtaining a biological sample, determining a level of an inhibin protein in said biological sample, and comparing said level to a normal mammal.

The claims of copending Application No. '352 is drawn to a method of monitoring for the onset or progress of an advanced neoplasm in a mammal comprising screening for the modulation the level of inhibitin in a biological sample derived from mammal wherein the levels of inhibin (α-inhibin) relative to the normal level of inhibin is indicate of the onset of progression of an advanced neoplasm, wherein the neoplasm is prostate, malignant, or metastatic neoplasm. It is noted that metastatic neoplasm is interpreted as one kind of developed cancers in this rejection.

Both set of the claims are drawn to a method for screening the level of α-inhibin for indicating the prostate cancer comprising the devolved cancer or advanced cancer. The difference is that the instant claims reciting the down regulation of α-inhibin and including the method steps of obtaining, detecting and comparing the inhibin levels in the sample (claims 72+) and the claims of '352 application do not recite the detailed method steps and encompass modulating the levels of α-inhibin, which would include the down regulated levels of α-inhibin. Thus, the difference between the two sets of the claims is the scope of claimed method. One having ordinary skill in the art would have been motivated with reasonable expectation of success to screen the changed or modulated levels of α-inhibin for indicating whether the individual having or not having a prostate cancer by down regulated levels of the α-inhibin in the sample of the patients and by the commonly used method steps of obtaining, detecting and comparing the levels of inhibin in the sample. Thus, the claims of instant application and the claims of '352 application are obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 58, 60, 62, 63, 69, 72-91, 93, 95, 96, 98 and 99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 18-20, 26, 27, 30, 33-38 and 40 of copending Application No. **11/578711 ('711)**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claim are directed to a method of enhancing cancer treatment by administering a compound of carbohydrate comprising

modified pectin in combination of another chemotherapeutic agent, thus the claims are obvious over each other.

Instant claims are drawn to a method of screening a mammal comprising screening for the down regulation of "inhibin protein levels" wherein the down regulation of the inhibin protein levels relative to the inhibin protein levels of a normal mammal is indicative of the mammal having developed prostate cancer, wherein the inhbin is α-inhibin. The claimed method is further defined as a method of screening a mammal for prostate cancer comprising the step of obtaining a biological sample and determining a level of an inhibin protein in said biological sample, and comparing said level to a normal mammal.

The claims of copending Application No '711 is drawn to a method of monitoring for the onset or progress of neoplasm in a mammal comprising screening for the modulation the level of inhibitin in a biological sample comprising serum, tissues derived from mammal wherein the levels of inhibin (α-inhibin) relative to the normal level of inhibin is indicate of the onset of progression of a neoplasm, wherein the neoplasm is prostate cancer, malignant neoplasm, wherein the levels of inhibin is decrease, the mammal is human.

Both set of the claims are drawn to a method for screening the level of α-inhibin for indicating the prostate cancer comprising the devolved cancer or onset or progression of a cancer. The difference is that the instant claims (claims 72+) reciting the method steps of obtaining, detecting and comparing the inhibin levels in the sample and the claims of '711 application do not recite the detailed method steps and encompass modulating the levels of α-inhibin which would include the down regulated levels of α-inhibin. Thus, the difference between the two sets of the claims is the scope of claimed method. One having ordinary skill in the art would have been motivated with reasonable expectation of success to screen the changed or modulated levels of α-inhibin for indicating whether the individual having or not having a prostate cancer by down regulated levels of the α-inhibin in the sample of the patients and by the commonly used method steps of obtaining, detecting and comparing the levels of inhibin in the sample. Thus, the claims of instant application and the claims of '711 application are obvious over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
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